Drop-outs due to Adverse Events: The 21 patients in whom the study therapy was prematurely discontinued due to an adverse event, are listed in the following table (NDA v.6.3,p.88).

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Adverse events leading to permanent discontinuation of study drug

Treatment regimen	Patient	Adverse event	Day* of onset	Intensity	Serious	Relation to study drug#
A1	801	Sepsis	4	severe	yes	no
	1001	Thrombocytopenia	4	severe	yes	no
	1202	Pulmonary embolus	14	severe	yes	no
	1601	Thyroid carcinoma	–	severe	yes	no
		Sepsis	4	severe	yes	no
		Multi organ failure	9	severe	yes	no
	1705	Coronary thrombosis	2	severe	yes	possible
	2201	Thrombocytopenia	34	severe	yes	possible
	3401	Shock	51	severe	yes	no
A2	4502	Multi organ failure	1	severe	yes	no
		Pulmonary embolus	1	severe	yes	no
B	501	Hemorrhage	2	severe	yes	possible
	505	Occlusion	2	moderate	yes	no
	506	Occlusion	1	moderate	yes	no
	507	Occlusion	2	severe	yes	no
	804	Hemothorax	25	moderate	yes	possible
		Hematuria	25	moderate	yes	possible
	1004	Ventricular fibrillation	5	severe	yes	no
	2101	Sepsis	68	severe	yes	no
	2703	Occlusion	2	mild	yes	no
		Hemorrhage	2	severe	yes	possible
	3201	Infection	11	moderate	no	no
	5201	Hematemesis	5	moderate	no	possible
	5501	Sepsis	14	severe	yes	no
C	701	Hemorrhage	1	moderate	yes	possible
	4301	Hemothorax	1	severe	yes	possible
		Hemothorax	1	severe	yes	possible
		Kidney failure	1	moderate	no	no
		Sepsis	2	moderate	no	no
		Anemia	4	no	no	no

* Relative to start of study treatment (Day 1). # According to investigator.

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Fatal AEs: Eleven patients died during the study. None of the deaths were considered possibly related to HBW 023 treatment or involved drug toxicity. The causes of death and assessment of relationship to treatment are shown below (v. 6.3, p.89)

AEs during repeated treatment courses: Six of eight patients who had repeated treatments with HBW 023 experienced AE (v.6.3,p.90).

Patients with fatal adverse events

Treatment regimen	Patient	Fatal adverse event	Day of onset	Relationship to study drug
A1	801	Sepsis	4	no
	1202	Pulmonary embolus	14	no
	1203	Heart failure	3	no
	1504	Apnea	17	no
	1601	Sepsis	4	no
		Multi organ failure	9	no
		Thyorid carcinoma	n.a.	n.a.
	1705	Multi organ failure	3	no
	3401	Shock	51	no
A2	4502	Multi organ failure	1	no
		Pulmonary embolus	1	no
B	1004	Ventricular fibrillation	5	no
	2101	Sepsis	1	no
		Sepsis	68	no
	5501	Sepsis	14	no

n.a. = not applicable

Adverse events in repeated treatment cycles with HBW 023

Patient No.	Cycle	Treatment regimen	Day of onset*	Adverse event	Intensity	Serious	Relation to study drug#
203	2	B	12	Hb decrease	mild	no	no
502	2	A2	4	SGOT increased	mild	no	possible
505	2	B	2	Occlusion/thromboembolism	moderate	yes	no
2201	2	A1	21	Hemothorax	severe	yes	no
			2	Hematuria	mild	no	possible
			6	Skin ulcer	severe	yes	no
			13	Rash	mild	no	possible
			34	Thrombocytopenia	severe	yes	possible
			48	Thrombocytopenia	mild	no	possible
			48	Thrombophlebitis	mild	yes	no
2701	2	B	2	Nail disorder	mild	no	no
	3	B	23	Occlusion/thromboembolism	severe	yes	no
	4	A2	4	Occlusion/thromboembolism	severe	yes	no
			7	Occlusion/thromboembolism	severe	yes	no
			8	Hb decrease	moderate	no	no
			11	Occlusion/thromboembolism	severe	yes	no
			14	Occlusion/thromboembolism	severe	yes	no
2702	2	B	3	Hemorrhage	severe	yes	possible
			10	Fever	mild	no	no
			12	Hb decreased	n.a.	no	n.a.

* Relative to start of study treatment (Day 1) in the respective cycle.

Bleeding events: Fifty-six patients (48.3%) experienced at least one bleeding event during the study. Twenty-one patients (18%) had a total of 32 major bleeding events. Seven patients had more than one major bleeding events.

A listing of major and minor bleeding events by treatment regimen is provided in the following table.

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Bleeding Events

Treatment Regimen	Number of patients	Major Bleeding N (%)	Minor Bleeding N (%)	Any Bleeding N (%)
A1	65	6 (9)	24 (37)	27 (61)
A2	4	1 (25)	4 (100)	4 (1000)
B	43	12 (28)	14 (33)	22 (51)
C	4	2 (50)	2 (50)	3 (75)
Total	116	21 (18)	44 (38)	56 (48)

The following types of major bleeding were observed:

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Bleeding at invasive sites (21 events in 16 patients)
- .peri- or post-operative bleeding (18 events)
- .internal bleeding due to trauma (2 events)
- .pre-existing hematoma (1 event)

Spontaneous bleeding (11 events in 5 patients)
- · urogenital bleeding (2 events)
- · naso-pharyngeal bleeding (2 event)
- · soft tissue bleeding (1 event)
- · gastrointestinal bleeding (5 events)
- · diffuse bleeding (1 event)

No intracerebral bleeding occurred during the study.

Overall, no age or gender differences were note for bleeding. High risk of bleeding was noted in patients with hypertension (11 major bleeding in 39 patients with hypertension).

The median aPTT at the time of major bleeding (27 events) was 2,01 fold control . The median HBW 023 plasma level was 219 ng/ml

Allergic reactions: Six patients experienced an allergic reaction (exanthema) during the study period. Three of the patients experiencing allergic reactions had positive anti-hirudin antibodies.

Laboratory investigations:

Hematoogv and clinical chemistrv

Hemoglobin: The majority of patients entered the study with Hgb value below the normal range. 31 of 112 patients (28%) with baseline value experienced a drop in Hgb of at least 1.2 mmol/l (2 g/dl) during treatment with HBW 023. The last measurement during treatment was similar to baseline in regimens A1, A2 and C; A significant reduction was observed for regimen B.

WBC: A significant reduction in WBC occurred during treatment in regimen A1 due to the baseline leukocytosis.

Platelets: The time courses of platelet counts has been discussed in the efficacy evaluation.

Serum creatinine: 24% patients entered the study with creatinine value above normal. Creatinine levels increased above normal in 8 patients during study treatment.

Coagulation

Activated partial thromboplastin time (aPTT): Median aPTT values increased within 4 hours of study drug (first scheduled determination) and remained within this range during treatment. In regimen C, median aPTT increased to 5.5 fold baseline at the start of CPB and remained at the end of surgery. The median aPTT was not affected by the concomitant administered of phenprocoumon in regimens A1, A2, and B.

Prothrombin Time: Most patients had normal PT at baseline. A consistent increase in PT was observed with institution of phenprocoumon therapy

Hirudin plasma levels and Thrombin-hirudin complexes (THC):

The results were similar to those reported in study B7.

Antibodies against hirudin:

Antibodies were positive at baseline in 1 patient who had received HBW 023 in study B7. 49 patients (42.2%) developed positive antibody (IgG) during the study. The first positive value was observed 4 days after the start of HBW 023; 26% of patients had antibodies by day 14 and 48% by day 28; 9 patients had antibodies at 6 month F/U. Antibodies were not clinically manifest.

HBW 023 clearance:

The results were similar to those reported in study B7.

IV. COMPARISON WITH HISTORICAL CONTROL

IV.A. EFFICACY RESULTS

All patients with **ongoing thrombosis** receiving HBW 023 in the treatment groups A1 and A2 of the prospective studies B7 (n=54) and NR13 (n=59) were eligible for comparison with the historical controls (n=91).

In study B7, eight patients who had cardiopulmonary bypass and 3 patients who had the diagnosis of HAT-II confirmed later than 21 days or at unknown time after the onset of clinical symptoms were excluded. None of these eleven excluded patients suffered a new TEC, amputation or death during the study period. Another 17 patients, who were treated according to treatment regimen B (without ongoing thrombosis), were not eligible.

In study NR13, four patients who had CPB and 9 patients who had diagnosis of HAT-II confirmed later than 21 days or at unknown time after the onset of clinical symptoms, 5 patients who started therapy later than 60 days after diagnosis, and 3 patients younger than 18 were excluded. None of these 21 excluded patients suffered a new TEC or death during the study period. One patient underwent a limb amputation during the study period. Another 36 patients, who were treated according to treatment regimen B (without ongoing thrombosis), were not eligible.

The primary prespecified analysis consisted of a comparison of the cumulative incidences of combined events since laboratory confirmation of HAT-II by means of a log-rank test.

Demographic and background characteristics: The sex distribution in the prospective study population and in the historical control was similar. The historical control patients were, on average, 7 years older than the patients in the prospective studies.

In study B7, 30 patients (55.6%) received heparin for medical conditions and 24 (44.4%) for surgery or trauma, in study NR13, 30 patients (50%) received heparin for medical conditions, 27 (46%) for surgery or trauma; in the historical control group, only 28 patients (30%) were from medicine and 63 (69.2%) were from surgery or trauma.

The platelet count at start of heparin treatment, the number of patients with thrombocytopenia during heparin treatment, the time to detection of thrombocytopenia and the median nadir platelet counts were comparable between historical control and prospective studies groups.

A summary is presented in the following table:

Platelet count prior to laboratory confirmation of HAT

	Study B7 HBW 023 (N=54)	Study NR13 HBW 023 (N=59)	Historical Control (N=91)
Platelet at start of heparin (G/I)			
no. of patients evaluable	51	54	73
median	221	241	231
mean	245	281	249
SD	120	143	108
Thrombocytopenia during heparin			
no. of patients evaluable	59	50	91
no. with thrombocytopenia	49(83.1%)	47(94.0%)	88(96.7%)
Time to detection of thrombopenia (days)			
no. of patients evaluable	56	50	88
25% quantile	4	6	8
median	9	9	11
75% quantile	15	12	14
Nadir platelet count (G/l)			
no. of patients evaluable	58	51	89
median	49	32	29
mean	87	57	39
SD	91	79	30
Platelet count at HAT confirmation (G/l)			
no. of patients evaiuable	56	51	80
median	70	68	63
mean	126	131	102
SD	141	143	109

More patients in the historical control group than in the HBW 023 studies had been treated with heparinoid and LMWH, as summarized below:

Recent heparin/heparinoid treatment before HAT confirmation

	Study B7 (N=54)	Study NR13 (N=59)	Historical Controls (N=91)
UFH	53 (98%)	57 (97%)	91 (100%)
Heparinoid	18 (33%)	20 (34%)	44 (48%)
LMWH	10 (18%)	8 (14%)	36 (39%)
At least one switch in heparin/heparinoid treatment	24 (44.4%)	24 (41%)	58 (63%)

The incidence rates of TECs and most frequently observed types of TECs(in >20% of patients with TEC) occurring during or after heparin therapy but prior to diagnosis of HAT-II in Study B7 and NR13 and in

the historical control are summarized in the following table.

TECs during heparin/heparinoid treatment before HAT confirmation

	Study B7 (N=54)	Study NR13 (N=59)	Historical Control (N=91)
TECs during heparin/heparinoid	N (%)	N (%)	N (%)
number of evaluable patients	54	56	90
number with TEC	44 (82)	41 (73)	80 (89)
Type of TEC*			
venous-distal	34 (77)	19 (46)	53 (66)
pulmonary embolism	23 (52)	19 (46)	35 (44)
venous-proximal	22 (50)	18 (44)	23 (29)
Arterial-peripheral	14 (32)	16 (39)	17 (21)

*Percentages refer to numbers of patients with TECs: patients may have had multiple TECs of multiple types.

Ten patients in study B7, 15 patients in study NR13 and 10 patients in the historical control group experienced TECs either after heparin/heparinoid therapy but before HAT-II confirmation, or after HAT confirmation but before selected treatment. Therefore, all 200 patients (54 + 56 + 90) had TEC at the start of selected treatment. The number of patients with TECs occurring during heparin/heparinoid treatment was higher in the historical control, however, more patients in the HBW 023 studies appeared to have multiple TECs complications.

Concomitant illnesses and medication: All patients had at least one concomitant illness. There were more documented concomitant illnesses in the historical control group than in the HBW 023 groups, however, in the historical control group, no distinction was made between concomitant and previous illnesses. No information was available concerning the severity of concomitant illnesses in any group. The most frequently affected ICD 9-CM main chapters (>=15% in any group) were as follows:

Concomitant and/or previous illnesses

ICD 9-CM main chapter	Study B7 (N=54)	Study NR13 (N=59)	Historical control (N=91)
Circulatory system	100%	100%	100%
Endocrine, metabolic, immune	28%	37%	64%
Musculoskeletal system Surgery	28%	34%	53%
Cardiovascular Surgery	20%	29%	37%
Respiratory System	20%	26%	32%
Neoplasm	19%	15%	7%
Injury and Poisoning	15%	25%	40%
Digestive System	13%	27%	25%
Musculoskeletal and Connective tissue	9%	24%	54%
Ill-defined Conditions	7%	27%	63%

Incidence of Clinical Events and comparison with historical control: The overall incidence of clinical events reported for the total population of patients entered in study B7, in study NR13 and in the historical control group are summarized in the following table.

Overall Incidence of Events Irrespective of Duration of Observation Period

Study B7		Study NR13		Historical controls	
No.of Patients (%)	82(100)	No.of Patients (%)	116(100)	No. of Patients (%)	91(100)
Deaths	6(7.3)	**Deaths**	11(9.5)	**Deaths**	11(12.1)
Amputations	3(3.7)	**Amputations**	10(8.6)	**Amputations**	8(8.8)
TECs	8(9.8)	**TECs**	20(17.2)	**TECs**	25(27.5)
Patients with Comb.Endpoint	**15(18.3)**	**Patients with Comb.Endpoint**	**33(28.4)**	**Patients with Comb. Endpoint**	**39(42.9)**

The incidence rates of clinical events reported for the patient population with HAT-II and thrombosis (treatment groups A1 and A2) and in the historical control are summarized in the following table.

Incidence of Events in relation to time of HAT-II diagnosis and start of HBW023 over the period of observation: patients with HAT-II and Thrombosis*

	Study B7		Study NR13		Historical Control
Event	Events After Start of HBW 023	Total Events from day of Diagnosis	Events After Start of HBW 023	Total Events from day of Diagnosis	Total Events from day of Dx
No.(%)	54 (100)	54 (100)	59 (100)	59 (100)	91 (100)
Death	3 (0.5)	5 (5.6)	8 (13.6)	8 (13.6)	11 (12.1)
Amput.	2 (0.4)	2 (3.7)	5 (8.5)	5 (8.5)	8 (8.8)
TECs	3 (5.6)	8 (14.8)	9 (15.3)	14 (23.7)	25 (27.5)
Comb. Events	**7 (12.9)**	**11 (20.4)**	**18 (30.5)**	**23 (38.9)**	**39 (42.9)**

*This table was constructed from the sponsors's data reported in the NDA Table C.2.1, v.1.113 and 6.4

Seven days after HAT-II confirmation, the cumulative combined event incidence of new TECs, limb amputations, and deaths in study B7 was 9.3% in the HBW 023 group and 21.5% in the historical control group.

On Day 35, when about 15% of patients were still at risk, it was 20.4% in the HBW 023 group and 52.0% in the historical control group. The log-rank test of combined events demonstrated a statistically significant difference in favor of HBW 023 treatment (p=0.0142)

In study NR13, the cumulative incidences of the combined endpoint after laboratory confirmation of HAT type II showed a numerical difference in favor of HBW023 treatment after day 21 since diagnosis, however, no statistically significant difference in incidence of events was noted between treated group and historical control.
The cumulative incidence rates of the combined events for the two prospective studies and for the historical control are summarized in the following table:

Cumulative combined event incidences since HAT confirmation

Time (Day since HAT confirmation)	Study B7 (n=54) No.at Risk	Study B7 (n=54) Cumulative Incidence	Study NR13 (n=59) No.at Risk	Study NR13 (n=59) Cumulative Incidence	Historical Control (n=91) No.at Risk	Historical Control (n=91) Cumulative Incidence
7	49	9.3%	46	23.7%	68	21.5%
14	44	18.5%	40	32.2%	49	31.7%
21	36	20.4%	31	35.8%	36	36.1%
28	12	20.4%	15	35.8%	23	43.1%
35	4	20.4%	5	35.8%	14	52.0%

Exploratory Analyses

Cox Regression Analysis of combined endpoint: The Cox regression analysis of combined endpoints showed that none of the prespecified prognostic factors (TECs during heparin treatment, age, sex, underlying disease, time between onset of symptoms and laboratory test) appeared to have a relevant influence on the combined event rate. In study B7, the unadjusted hazard ratio (HBW 023: historical control) was 0.44 (95% CI 0.23-0.87; p-value 0.012). Adjusting for prognostic factors, the estimated hazard ratio was 0.44 (95% CI 0.21-0.91; p-value=0.019). In study NR13, the unadjusted comparison between HBW 023-treated and historical control groups shoed no statistical significance (p=076). The unadjusted hazard ratio (HBW 023: historical control) was 0.922 (95% CI 0.548-1.55). Adjusting for prognostic factors, the estimated hazard ratio was 0.94 (95% CI 0.534-1.65, p-value=0.83).

Combined endpoint of amputation and death: This analysis included two hard endpoints which were not subject to misclassification errors: limb amputation and death. The results from study B7 and NR13 and from the historical control group are summarized in the following table

Cumulative combined incidences of amputation or death since HAT confirmation

Time (Day since HAT confirmation)	Study B7 (n=54) No.at Risk	Study B7 (n=54) Cumulative Incidence	Study NR13 (n=59) No.at Risk	Study NR13 (n=59) Cumulative Incidence	Historical Control (n=91) No.at Risk	Historical Control (n=91) Cumulative Incidence
7	53	1.9%	53	10.2%	79	4.5%
14	49	7.5%	48	18.6%	64	10.9%
21	42	7.5%	39	20.3%	49	12.4%
28	16	7.5%	22	20.3%	32	17.4%
35	6	7.5%	6	20.3%	21	23.4%
42	3	7.5%	5	20.3%	20	27.1%
49	1	7.5%	3	20.3%	13	36.2%

Non-prespecified exploratory analyses

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Combined endpoint by first selected treatment after HAT confirmation:
The first prescribed treatment after confirmation of HAT type II was identified for each historical control patient and all events occurring during such treatment were compared with those occurring during HBW 023 treatment. Treatment could not be assigned for 14 historical control patients. For the 77 evaluable control patients, the first treatment included Orgaran in 24 patients, phenprocoumon in 21 and no treatment or combined treatments in 32.

The mean duration of treatment in the historical control group was 14.9 days compared to 12.5 days for the HBW 023 group.
Three additional patients in the historical control group were excluded: 2 because of incomplete time to event data and 1 because treatment was given for only one day. Therefore, 74 historical control patients were subject to analysis.

The cumulative endpoint incidences for each prospective study and for the historical control are summarized in the following table.

Cumulative combined event incidences during first selected treatment

Time (Day since HAT confirmation)	Study B7 (n=54) No.at Risk	Study B7 (n=54) Cumulative Incidence	Study NR13 (n=59) No.at Risk	Study NR13 (n=59) Cumulative Incidence	Historical Control (n=74) No.at Risk	Historical Control (n=74) Cumulative Incidence
1	54	1.9%	57	3.1%	74	8.1%
3	53	3.7%	54	8.6%	55	15.6%
7	45	3.7%	43	17.9%	37	21.3%
17	11	6.1%	17	33.2%	18	31.8%
28	3	6.1%	4	33.2%	7	40.3%

The cumulative incidence of the combined endpoints was significantly higher in the historical control group than in the HBW 023 group treated in study B7 (p=0.0014, log-rank test). The likelihood ratio test for the comparison of the two groups adjusted for prognostic factors showed a statistically significant difference in time to combined endpoint (p=0.0043). The estimated hazard ratio for the HBW 023: historical control was 0.21 (95% Cl 0.058-0.72).
None of these analyses were statistically significant in study NR13.

The incidence of events reported with HBW 023 treatment was compared to that reported with each of the first selected treatments in the historical controls. In study B7, the risk of combined endpoints was significantly lower in the HBW 023-treated group compared to historical control patients treated with heparinoid (p=0.0004) or with ongoing phenprocoumon (p=0.013). The cumulative incidence of death was numerically lower in the HBW 023 group than in the Heparinoid group (p=0.093); the incidences of TECs were significantly higher in the Heparinoid group (p=0.0008) and in the phenprocoumon group (p=0.0055) than in the HBW 023 group. The cumulative incidences of limb amputation were similar in the two groups (p=0.85).

In study NR13, no significant differences were noted between the HBW 023 group and any of the historical control first selected treatment groups. The cumulative incidence of death was numerically higher in the heparinoid group after day 14; new TECs rates were higher in the pooled historical control and in the heparinoid group; the rate of limb amputation was higher in the HBW 023 group that in the heparinoid group. No deaths or limb amputations occurred with phenprocoumon.

IV.B. SAFETY RESULTS

Cumulative incidence of bleeding events: The most frequently observed bleeding events are summarized in the following table:

Bleeding events observed in more than 2% of patients in either group

HARTS term	Study B7 (N=54)	NR13 (N=59)	Historical Control (N=91)
Hemorrhage	7(13%)	11(19%)	5 (5%)
Anemia		7 (12%)	0 (0%)
Decreased hemoglobin	2(4%)	4 (7%)	1 (1%)
Epistaxis		4 (7%)	1 (1%)
Hematuria	2(4%)	3 (5%)	0 (0%)
Rectal hemorrhage	2(4%)	2 (3%)	1 (1%)
Vaginal hemorrhage		2 (3%)	0 (0%)
GI hemorrhage	0	1 (2%)	5 (6%)
Injection site hemor.	4(8%)	1 (2%)	2 (2%)
Cerebral hemorrhage	0	0 (0%)	2 (2%)
Hemoptysis	1(2%)	0 (0%)	2 (2%)

Cumulative incidences of documented bleedings, documented bleedings or transfusions, and bleedings requiring transfusions are summarized in the following table.

Cumulative bleeding events since HAT confirmation

	B7 (N=54)		NR13 (N=59)		Historical control (N=90)*	
	No.at Risk	Cumul. Rate	No.at Risk	Cumul. Rate	No.at Risk	Cumul. Rate
Documented bleedings						
Day 7	41	26%	40	33%	72	11%
Day 14	39	28%	33	36%	56	17%
Day 28	12	30%	11	43%	25	21%
B7 vs HC+:p=0.16						
NR13 vs HC:p=0.0009						
Bleedings or transfusions						
Day 7	37	33%	35	43%	59	23%
Day 14	35	37%	28	46%	47	27%
Day 28	11	39%	8	54%	20	30%
B7 vs HC:p=0.29						
NR13 vs HC:p=0.0025						
Bleedings + transfusions						
Day 7	48	13%	47	19%	77	5%
Day 14	45	13%	41	23%	62	7%
Day 28	14	13%	17	23%	29	7%
B7 vs HC:p=0.24						
NR13 vs HC:p=0.0024						

*date of bleeding not available for one patient.
+ HC= Historical Control

The classification of bleeding shown in the above table was used to allow a comparison between treated groups and historical control as no other definition of bleeding was available for the historical control. In summary, a statistically significant higher overall bleeding rate was observed in the HBW 023 group as compared to the historical control in study NR13. However, severe bleedings, such as GI hemorrhage or cerebral hemorrhage, appeared to be more frequent in the historical control group.

Overall, complications other than thromboembolic events and bleeding occurring after laboratory confirmation of HAT were less frequent in the treated groups than in the historical control.

Laboratory variables: The mean increase in platelet counts per day between laboratory confirmation of HAT and ten days thereafter was estimated for each patient as a slope of a linear regression model.

The increase in platelet counts was comparable between the HBW 023 group (mean 25.8 G/l per day, SD 21.0 G/l) and the historical control group (mean 23.4 G/l per day, SD 20.3 G/l).

Mean aPTT values during the first ten days after laboratory confirmation of HAT were considerably higher in the HBW 023 group (mean 63.5 seconds, SD 12.9 seconds) than in the historical control group (mean 43.6 seconds, SD 13.3 seconds) as expected since patients in the historical control group received anticoagulant treatment with no or only minor effect on aPTT (phenprocoumon, heparinoid, ASA) or no anticoagulation at all.

Mean PT values within ten days after HAT confirmation were slightly higher in the HBW 023 group (mean 63%, SD 12%) compared with the historical control group (mean 48%, SD 24%) due to a large number of patients receiving phenprocomuon in the historical control group.

V. META-ANALYSIS OF STUDIES B7 AND NR13

The aim of the meta-analysis was to combine all available data of HAT patients with thrombosis treated with HBW 023 and to compare the clinical outcome of these patients with that of the historical control. Clinical outcome included death, amputation, new TECs, and bleeding events. In addition, the clinical outcome of patients grouped into three different APTT classes (low, medium and high: APTT ratio <1.5, <3.0, or >3.0 respectively) was assessed in order to identify the range of anticoagulation that results in optimal risk/benefit ratio for HBW 023 therapy of HAT patients with thrombosis.

The data from the two prospective studies were pooled according to three time periods: pre-treatment, treatment, and post-treatment interval. Since no effect of HBW 023 coould be expected during the pre-treatment period, the "start of treatment" was considered as the most relevant starting point for the comparison with the historical control. The product-limit method of K-M was used to estimate the combined rates of events, depending on the time since confirmation of HAT diagnosis for both HBW 023 groups and historical control group. To account for differences in lengths of observation periods, time-to-event analysis was performed.

Analysis of Events in the period "After HAT confirmation": The weekly cumulative incidences of combined events from the time of laboratory diagnosis of HAT-II until the end of the observation period are summarized in the following table.

Cumulative combined event incidences since HAT confirmation

Time (Days since HAT confirmation) confirmation)	HBW 023 (n=113) No.at Risk	Cumulative Incidence	Historical Control (n=91) No.at Risk	Cumulative Incidence
7	95	16.8%	68	21.5%
14	84	25.7%	49	31.7%
21	67	28.4%	36	36.1%
28	27	28.4%	23	43.1%
35	9	28.4%	14	52.0%
42	5	40.3%	13	55.5%

Log-rank test

The combined incidence of events was lower in the treated group compared to historical controls, however, the difference was not statistically significant (p-value=0.11).

Analysis of events in the period after start of treatment: The log-rank test estimate of the cumulative incidence of combined events occurring during the treatment period (from start to end of treatment) showed a borderline statistically significant reduction of combined event rates in pooled treated patients compared to historical controls (p=0.049).

When the cumulative incidence of the combined events occurring from the time of start of therapy to end of follow-up period (≤ 60 days) in the pooled treated group was compared to the historical control group, the difference was statistically significant in favor ot HBW 023 treatment (p-value=0.004).

The results are summarized in the following table (NDA v. 6.2, p.22)

Cumulative combined event incidences from start of Therapy to end of observation

Time (Days since start of therapy)	HBW 023 (n=113) No.at Risk	Cumulative Incidence	Historical Control (n=74) No.at Risk	Cumulative Incidence
7	102	10.6%	55	24.9%
14	92	19.5%	38	36.1%
21	76	21.3%	28	38.0%
28	27	21.3%	20	40.7%
35	9	21.3%	12	47.8%
42	6	21.3%	11	52.2%

Log-rank test

The cumulative incidence of death and limb amputation showed no statistically significant difference between the two groups. The cumulative incidence of death at day 35 was numerically lower in the HBW 023 pooled group compared to the historical control (8.9% vs 17.6%). A statistically significant difference between the two groups was observed for incidence of new TECs: 6.3% on day 7 and 10.1% on day 35 for the HBW 023 pooled group compared to 22.2% and 27.2% respectively in the historical control group (p-value=0.005).

Meta-Analysis of Bleeding Events: Statistically significant higher incidences of any bleeding events (log-rank test p=0.001) and of bleeding requiring transfusion (log-rank test p=0.02) were observed in the HBW 023 pooled group compared to the historical control group.

The cumulative incidences of bleeding events requiring transfusion for the first 6 weeks are summarized in the following table (NDA v.6.2, p.23).

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Cumulative incidences of Bleeding requiring Transfusion from start of Therapy

Time (Days since start of therapy)	HBW 023 (n=113) No.at Risk	HBW 023 (n=113) Cumulative Incidence	Historical Control (n=74) No.at Risk	Historical Control (n=74) Cumulative Incidence
7	93	17.0%	67	4.1%
14	85	18.8%	53	7.1%
21	71	18.8%	40	7.1%
28	24	18.8%	26	7.1%
35	9	18.8%	16	7.1%
42	5	18.8%	16	7.1%

An overall summary of the clinical outcome, in terms of both efficacy endpoints and bleeding complications, from the start of therapy to the end of the observation period are summarized in the following table (NDA v.6.2, p.22)

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Crude incidences of clinical endpoints from start of therapy to end of observation

	Study B7 (N=54)		Study NR13 (N=59)		Combined (N=113)		Hist. Control (N=77)	
Event	N	%	N	%	N	%	N	%
Death	3	6%	8	14%	11	10%	9	12%
Amputation	2	4%	5	8%	7	6%	6	8%
New TECs	3	6%	9	15%	12	11%	19	25%
Combined	7	13%	18	31%	25	22%	30	40%
Bleeding + Transfusion	7	13%	14	24%	21	19%	5	6%
Any Bleeding	16	30%	25	42%	41	36%	12	15%

VI. INTEGRATED SUMMARY OF SAFETY

The following clinical trials are included in the ISS.

Study Category	No. of Studies	No of Subjects
Clinical Pharmacology Studies, Phase I:	23	311
HAT-II	2	198
Acute MI + thrombolytics	4	530
ACS without thrombolytics	3	249
Therapy and Prophylaxis of DVT	4	149
Other Inducations	1	20
TOTAL	37	1457

As of April 1996, a total of 1457 patients have received at least one dose of Lepirudine. The clinical indications studied included HAT-II, Acute MI, Unstable Angina (UA), DVT, and DIC.
All patients who received at least one dose were included in the safety analyses. AE were assessed for severity and attribution.
The most relevant AE expected with therapy with r-hirudin ws bleeding and allergic reactions.

Due to wide differences among clinical indications, the adverse events are grouped according to indication. Pooling across studies was done only for allergic reactions.

Assessment of bleeding waried in different studies, therefore a common definition of major bleeding eas established for the ISS identifying overt and non-overt bleeding as:

- Overt Bleeding was defined as major if:
  - . required transfusion of at least 2 units of blood, or
  - . required a surgical intervention, or
  - . was a serious AE.
- Non-overt bleeding was defined as major if:
  - . it was intracranial, or
  - . required thransfusion of at least 2 units of blood,or
  - . a drop in Hgb of >2 g/l was observed between the start of study treatment and the first transfusion.

This reassessment of major bleeding led to reassignment of 12 patients to major bleeding and 23 patients non-major bleeding.

Allergic reactions were redifined to include all symptoms possibly indicating an allergic reaction.

The ISS comprises an overview of deaths, serious AE (SAE), AE and discontinuations due to AE. The HARTS terminology was used for coding AE. For ongoing studies, only SAE have been included in the ISS.

Excluding the 23 Phase I studies and the two HAT-II clinical trials which have been evaluated for safety in this NDA review, 948 patients are included in this ISS.

A total of 34 died (3.6%); 147 experienced at least one SAE (14.3%); and 81 patients (8.8%) discontinued therapy due to AE.

The AE reported in the study populations and included in the ISS were:

Adverse Events* (Aes)	Distribution No.	%
Patients with AEs	515	54
Possibly Related AE	314	33
Serious AE (SAE)	121	13
Possibly related SAE	52	6
Deaths due to AE	28	3
Deaths due to possibly related AE	11	1
AE leading to discontinuation	154	16
Possibly related AE leading to discont.	86	9
Permanent discontinuation due to AE	83	9

*A patient may have experienced multiple events

The greatest number of major bleeding events occurred in HAT-II patients (13%); minor bleeding was more frequent in conjunction with thrombolytics (44%), the incidence of minor bleeding in indications without thrombolytics was 20%.

Possible allergic reactions were reporterd in 15 patients (1.5%), anaphylaxis and anaphylactoid reactions were reported for 7 patients (0.7%). Most of the allergic reactions occurred in patients receiving SK or undergoing angiography. Two HAT-II aptients experienced allergic reactionas attributed to Lepirudin.

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VI.A. ADVERSE EVENTS

Adverse events in Phase I studies: No SAE occurred in Phase I trials in normal and renal insufficiency patients.

Adverse events occurring in Acute MI with thrombolytics: A total of 530 AMI patients were treated with Lepirudin in completed studies and 735 patients have been enrolled in the ongoing study NR11.
Major bleeding occurred in 46 patients (9%) and minor bleeding in 235 patients (44%). Possible allergic reactions were reported in 19 patients (4%), of these 11 were attributed to Lepirudin
The SAE reported in the completed studies are summarized in the following table (NDA, ISS, v.1.138, p.72).

Summary of adverse events

	Studies B1 -B3 (N=490)		Study NR1 (N=40)		Total (N=530)	
	Total	Possibly related	Total	Possibly related	Total	Possibly related
Patients with						
- AEs*	314 (64%)	215 (44%)	31 (78%)	18 (45%)	345 (65%)	233 (44%)
most frequent+:						
Inj. site hemorrhage	146 (30%)	135 (28%)	7 (18%)	7 (18%)	153 (29%)	142 (27%)
Angina pectoris	45 (9%)	5 (1%)	15 (38%)	6 (15%)	60 (11%)	11 (2%)
Ventr. tachycardia	33 (7%)	6 (1%)	3 (8%)	3 (8%)	36 (7%)	9 (2%)
Bradycardia	23 (5%)	4 (1%)	2 (5%)	1 (3%)	25 (5%)	5 (1%)
- SAEs**	91 (19%)	43 (9%)	8 (20%)	3 (8%)	99 (19%)	46 (9%)
most frequent+:						
Injection site hemorrhage	18 (4%)	17 (4%)	0 (0%)	0 (0%)	18 (3%)	17 (3%)
Angina pectoris	13 (3%)	1 (0.2%)	1 (3%)	1 (3%)	14 (3%)	2 (0.4%)
- fatal SAEs	23 (5%)	10 (2%)	1 (3%)	1 (3%)	24 (5%)	11 (2%)
Cardiogenic shock	6 (1%)	0 (0%)	0 (0%)	0 (0%)	6 (1%)	0 (0%)
cerebral hemorrhage	5 (1%)	5 (1%)	0 (0%)	0 (0%)	5 (1%)	5 (1%)
ventricular rupture	5 (1%)	2 (0.4%)	0 (0%)	0 (0%)	5 (1%)	2 (0.4%)
- discontinuations due to AEs	64 (13%)	50 (10%)	1 (3%)	0 (0%)	65 (12%)	50 (9%)
Inj. site hemorrhage	30 (6%)	27 (6%)	0 (0%)	0 (0%)	30 (6%)	27 (5%)

* including SAEs
** including fatal SAEs
\+ most frequently observed events

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Adverse Events in patients with ACS without concomitant thrombolytics.
A total of 249 patients with UA were enrolled in completed studies and 836 have been enrolled in ongoinbg studies.
A total of 90 patients with AMI have been enrolled in study NR12.
The AE reported in completed studies are summarized in the following table (NDA, ISS, v.1.138, p.74). Major bleeding occurred in 3 patient (1%) and minor bleeding in 49 (20%). Possible allergic reactions were reported in 7 patients (3%), of these, 2 were considered possibly related to Lepirudin.

Summary of adverse events
(excluding non-fatal MI, cardiogenic shock, angina pectoris, chest pain)

	Studies B4 and B5# (N=206)		Study NR2 (N=43)		Total (N=249)	
	Total	Possibly related	Total	Possibly related	Total	Possibly related
Patients with						
- AEs*	93 (45%)	43 (21%)	22 (51%)	10 (23%)	115 (46%)	53 (21%)
most frequent+:						
Headache	42 (20%)	9 (4%)	0 (0%)	0 (0%)	42 (17%)	9 (4%)
Inj. site hemorrhage	9 (4%)	9 (4%)	3 (7%)	2 (5%)	12 (5%)	11 (4%)
Dyspepsia	10 (5%)	2 (1%)	0 (0%)	0 (0%)	10 (4%)	2 (1%)
Nausea	8 (4%)	3 (2%)	0 (0%)	0 (0%)	8 (3%)	3 (1%)
- SAEs**	10 (5%)	1 (0.5%)	5 (12%)	3 (7%)	15 (6%)	4 (2%)
most frequent+:						
GI hemorrhage	0 (0%)	0 (0%)	2 (5%)	2 (5%)	2 (1%)	2 (1%)
- fatal SAEs	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
- discontinuations due to AEs	7 (3%)	5 (2%)	5 (12%)	3 (7%)	12 (5%)	8 (3%)
most frequent+:						
Kidney function abnormal	0 (0%)	0 (0%)	2 (5%)	0 (0%)	2 (1%)	0 (0%)

\# only data from the interim analysis were included in this table
* including SAEs
** including fatal SAEs
\+ most frequently observed events

Adverse Events in patients receiving DVT therapy of Prophylaxis.
A total of 149 patients have received Lepirudin. Six patients (4%) experienced major bleeding and 25 experienced minor bleeding.

The AE reported are summarized in the following table (NDA, ISS, v.1.138, p.75).

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Summary of adverse events

	Study B6 (N=118)		Studies NR3, NR4 and NR5 (N=31)		Total (N=149)	
	Total	Possibly related	Total	Possibly related	Total	Possibly related
Patients with						
- AEs*	33 (28%)	21 (18%)	10 (32%)	3 (10%)	43 (29%)	24 (16%)
most frequent+						
Injection site hem-orrhage	14 (12%)	12 (10%)	0 (0%)	0 (0%)	14 (9%)	12 (8%)
Pulmonary embolus	5 (4%)	3 (3%)	1 (3%)	1 (3%)	6 (4%)	4 (3%)
- SAEs**	6 (5%)	1 (1%)	1 (3%)	1 (3%)	7 (5%)	2 (1%)
Pulmonary embolus	2 (2%)	1 (1%)	1 (3%)	1 (3%)	3 (2%)	2 (1%)
- fatal SAEs	2 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
- discontinuations due to AEs	5 (4%)	3 (3%)	1 (3%)	1 (3%)	6 (4%)	4 (3%)
Pulmonary embolus	2 (2%)	2 (2%)	1 (3%)	1 (3%)	3 (2%)	3 (2%)

* including SAEs
** including fatal SAEs
\+ most frequently observed events

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Adverse Events in patients treated for Other Indications
A total of 20 patients have received Lepirudin for Hemodialysis. Of these patients, 12 (60%) experienced AE, including 4 thrombotic events, 2 of which occurred in the dialysis tubing. Four AE were considered drug-related. No patients experienced serious AE or discontinued therapy due to AE.

Six patients with DIC have been treated with Lepiridin in a completed Japanese study and 10 patients were enrolled in an ongoing study of DIC. Four patients experienced bleeding at baseline.

VI.B. DEATHS, DROP-OUTS AND OTHER SERIOUS ADVERSE EVENTS

Phase I studies: Three normal subjects discontinued treatment due to increased aPTT, one kidney patients for extravasation of infusion.

Treatment with Lepirudin in conjunction with thrombolytics: A total of 23 patients (4.7%) in the controlled studies died. Cause of death included VPB, cardiac tamponade, cardiogenic shock, reinfarction, arrhythmia, major bleeding, intracerebral bleeding, ischemic stroke, URT bleeding.
A total of 64 patients discontinued treatment due to AE. Bleeding was the most frequent AE.
In uncontrolled studies, one patients dies of retroperitoneal bleed and 7 patients experienced cardiac SAE. One patient discontinued treatment due to AE.
In one ongoing double-blind study (NR11), the total SAE are reported blinded. A total of 146 patients have experienced SAE, including 46 deaths. A total of 34 SAE were attributed to treatment. Most SAE were cardiac.

Treatment of ACS without concomitant thrombolytics: Two patients from 249 died (1%) and 15 experienced SAE (6%). Four SAE were attributed to treatment. Twelve patients discontinued treatment due to AE.
In the ongoing study B5, 13 patients have died, 7 of whom were treated with Lepirudin. SAE occurred in 50 patients treated with Lepirudin, 26 treated with heparin, and 6 patients with blinded treatment. Unexpected SAE occurred in 11 Lepirudin patients (3.1%), 8 heparin patients 93.250, and 4 on blind treatment (1.8%).
In the ongoing study NR12, 5 patients have died (6%), 64 have experisnced AE, of which 32 were SAE and 8 unexpected.

Therapy or Prophylaxis of DVT: Two of 149 treated patients died and 7 experienced SAE (5%). Six patients discontinued treatment due to AE.

Treatment of DIC: Two patients died after treatment due to the underlying disease.

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VI.C. LABORATORY DATA

Laboratory changes affected hemoglobin and hematocrit as result of the bleeding associated with the use of HBW 023 and the aPTT values as result of the anticoagulant activity of HBW 023.
Special coagulation paramenters (PF_{1-2}, TAT, anti-Xa, hirudin levels, THC) were dose-dependent and reflected the effect of hirudin on the

underlying condition-relayed changes of hemostasis.

The incidence rates of anti-hirudin antibodies varied in different studies, the highest incidence occurred in HAT-II patients. The developed of antibodies did not appear to be dose-related. The development of anti-hirudin antibodies influenced the PK of HBW 023 by leading to prolonged elimination requiring dose reduction.

VI.D. SUBSET ANALYSES

Factors associated with increased risk of bleeding: Older patients and female patients experienced more frequent and more severe bleeding complications. Frequency of major bleeding was also associated with underlying conditions such as HAT-II, renal insufficiency.

Dose-Response Relationship: Bleeding events were dose-related. Major bleeding events occurred in HAT-II patients treated with the highest claimed dose (treatment regimen A1).

Drug-Interactions: The risk of major bleeding was clearly higher in patients treated with HBW 023 in conjunction with thrombolysis, particularly in association with other risk factors such as age and female gender.

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VII. ANALYSIS OF APTT-CLASS/EFFECT RELATIONSHIP

The two clinical outcome represented by 1) the combined efficacy endpoints (death, amputation, new TECs) and, 2) the occurrence of any documented bleeding, were assessed in relation to aPTT values achieved during the study period.

The aPTT values were separated in three classes: 1-1,5, 1.5-3.0, and >3.0 times control value. The analysis included 204 patients: 91 historical control and 113 pooled HBW 023-treated. Both clinical endpoint models revealed a statistically significant contribution of the selected covariates to the goodness of fit ($p < 0.05$).

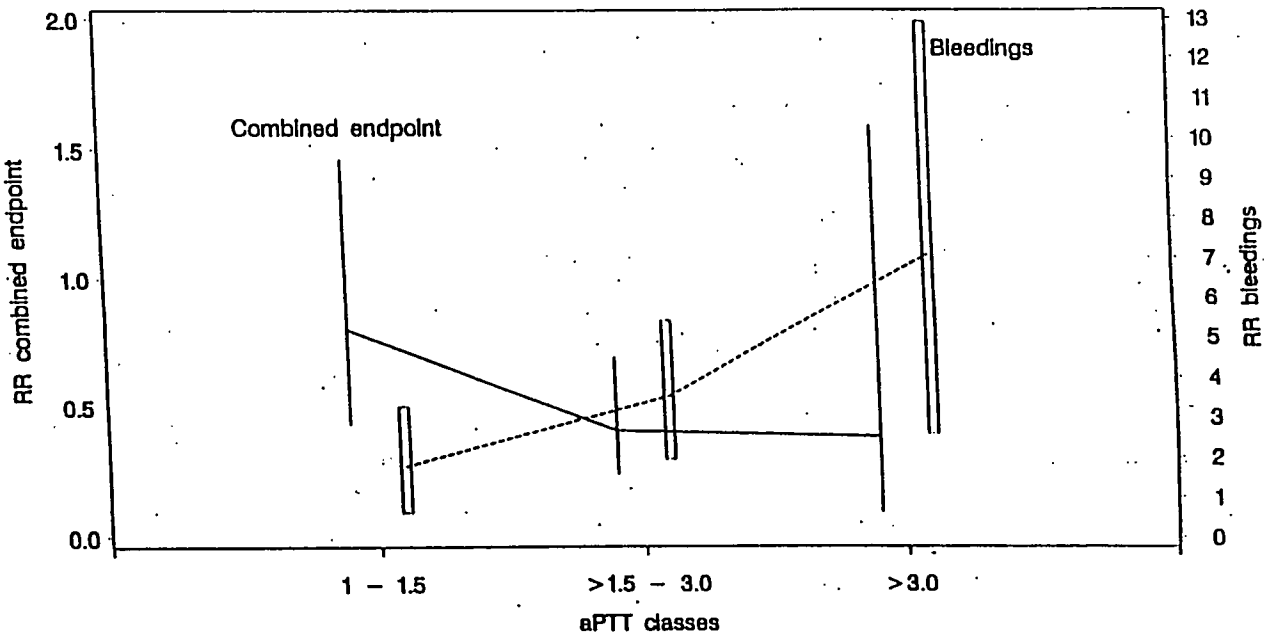
Medium aPTT-level (1.5-3.0) was associated with a significant reduction of combined efficacy (Risk ratio 0.42, $p=0.009$). Lower aPTT-level (>1-1.5) was associated with a week and non-significant reduction of events (risk ratio 0.86, $p=0.72$). Higher aPTT-level (>3.0) did not show further improvement of

events compared to medium aPTT-level (risk ratio 0.70, p=0.56).

The aPTT level showed a strong association with the risk of bleeding; low aPTT did not significantly increase the risk of bleeding (risk ratio 1.57, p=0.4). At medium aPTT-level, the risk ratio was 3.21 (p=0.0003) and increased to 6.03 (p=0.0002) at high aPTT level. None of the other covariates showed a statistically significant association with bleeding risk (p>1).

In conclusion, the risk/benefit appears to be optimal at medium aPTT levels
The results are shown in the following graph (NDA v.6.2, p110)

Figure 2.A: Risk ratios of combined endpoint and bleeding per aPTT class with corresponding 95% confidence limits



VIII. SUMMARY AND CONCLUSIONS

Patients with the immune type of heparin-induced thrombocytopenia (HAT-II) presenting with thrombosis are at increased risk of new thrombotic complications which may lead to limb amputation in 10-20% of patients or result death in of patients.

Patients with HAT-II presenting with isolated thrombocytopenia are also at high risk of TECs despite the fact that thrombocytopenia usually recovers following heparin discontinuation. As shown recently in a 14 year study of HAT-II, the incidence of TECs in patients with isolated thrombocytopenia approaches 50% over the 10 to 30 days after discontinuation of heparin. In this study, the mortality rate was approximately 20% for both HAT-II groups with or without thrombosis.

No satisfactory antithrombotic regimen is currently available for the management of HAT-II patients in need of anticoagulation for ongoing thrombosis or for prophylaxis of thromboembolic complications. Of the available anticoagulant drugs, the Low Molecular Weight Heparins (LMWH) cross-react with anti-heparin antibodies with a frequency that approaches 100% and warfarin does not provide immediate anticoagulation. The heparinoid Orgaran has shown lower cross-reactivity with anti-heparin antibodies than LMWH, but its efficacy has not yet been determined.

Two prospective, open, multicenter Phase III clinical trials were carried out by Berhingwerke AG to evaluated the efficacy and safety of a recombinant hirudin (HBW 023) in patients with confirmed heparin-associated thrombocytopenia.

The two clinical trials were based on the documented anti-thrombin activity of r-hirudin and on its lack of cross-reactivity with anti-heparin antibodies. In view of this preliminary information and because of the severity of indication, a comparison of HBW 023 to placebo was considered unethical. Furthermore, it was not possible to perform a controlled trial of HBW 023 with an active comparator, as no therapy is currently available or approved in Europe or in the United States for this condition. Consequently, the clinical studies of HBW 023 in HAT-II were originally planned as prospective, open, uncontrolled trials to test the hypothesis whether iv. treatment with HBW 023 provided effective anticoagulation without continuation of the underlying immunological process.

The primary objective of the study was to demonstrate adequate anticoagulation as assessed by aPTT prolongation, and recovery of

thrombocytopenia in patients with acute HAT-II or maintenance of normal baseline platelet counts in patients with latent HAT-II (primary efficacy endpoint). The assessment of the primary efficacy was based on surrogate endpoint of anticoagulation (aPTT prolongation) and of platelet recovery (platelet counts) over time using the patient baseline as comparison.
As secondary objectives, the combined and individual incidences of arterial or venous thromboembolic complications (TECs), limb amputations, and deaths were analyzed (secondary endpoint). The clinical events were defined as secondary endpoints since a direct comparison of these events could not be made due to lack of an approved control treatment.
The incidence of major bleeding events was assessed.

At a pre-NDA meeting held on 4-11-1996 with FDA representatives, the Agency pointed out the limitations of surrogate endpoints and the need to establish the efficacy and safety of HBW 023 on the clinical events rather than on surrogate endpoints of platelet count and aPTT values. Therefore, the Agency recommended that the clinical events (death, amputation and new TECs) in the study population treated with HBW 023 be compared, in a post-hoc analysis, with an historical control of patients with HAT-II untreated or treated with any non-approved treatments. The Agency also recommended to focus on the patients with HAT-II and thrombosis for the comparison of clinical events; namely, to compare the clinical events occurring in patients presenting with thrombosis, i.e., patients in treatment regimens A1 and A2 of the prospective study to the historical control consisting of patients with HAT-II and documented thrombosis at the time of laboratory diagnosis.

NDA 20-807, based on the results of Study B7, was submitted on 3-30-1997. On May 5, 1997, the sponsor submitted an Information Amendment with the results of a second study that was ongoing at the time of the NDA submission, study NR13. The two studies were nearly identical for study design, primary and secondary objectives, treatment regimens, as well as for general study outline and organization. In both studies, the clinical events were compared to the same historical control consisting of 91 evaluable patients who were identified from three registries of 182 cases of heparin-induced thrombocytopenia from 51 German hospitals.

The two clinical trials were performed in Germany from March 1994 to April 1996. Both studies were performed by Dr. Greinacher as principal investigator, however, the total patient population of 198 patients was enrolled by several investigators from more that 45 centers for each study and from multiple geographical locations. Dr. Greinacher is an internationally known expert on the

pathophysiology of HAT-II and is an expert on the laboratory diagnosis of anti-heparin antibodies.

The studies were acceptable since there is no evidence that the patient population or the diagnosis and management of HAT-II in Germany differs from the US.
The studies were well conducted and in accordance with acceptable ethical principles. The principal investigator's study site was inspected by the Agency's DSI (Dr. R.Young). All records were located and all data requested were made available for inspection.

A total of 82 patients were enrolled in study B7 and 116 patients in study NR13. In both studies, 4 groups of patients were treated with HBW 023:

Group A1= Patients with HAT-II and thrombosis without thrombolytics
Group A2= Patients with HAT-II and thrombosis receiving thrombolytics
Group B= Prophylaxis of venous or arterial thromboembolism
Group C= Anticoagulation during cardiopulmonary bypass (CPB).

In groups A1, A2, and B, treatment was scheduled for 2-10 days; in group C, treatment was limited to the CPB. If needed, patients could be treated for longer periods of time, could be re-treated or could be switched from treatment group B to A. The study period for assessment of primary efficacy endpoint was completed by day 24 or 14 days after end of treatment. The median duration of study treatment for patients with acute HAT-II was 10-11 days.

For patients requiring prolonged anticoagulation, the administration of HBW 023 was gradually decreased during the switch to oral anticoagulant therapy and was discontinued once adequate PT or INR were achieved. A total of 64 patients were started on oral anticoagulant during administration of HBW 023. The most frequently used oral anticoagulant was phenprocoumon (Marcumar). This vit. K-inhibitor is not used in United States where warfarin is the most widely used oral anticoagulant. The two compounds have different pharmacokinetics, however, as attested by an independent expert (Dr. J Hirsh, Director, Hamilton Civic Hospital Research Center, Hamilton, Ontario), both are coumarin derivatives with identical mechanism of action of impairing vit.K-dependent clotting factors, both are used for the same indications, and both are monitored by the PT using the same targeted INR.

The efficacy of the treatment with HBW 023 was assessed on the "primary endpoint" by protocol criteria of anticoagulation and platelet recovery and on the clinical endpoint of new thromboembolic complications (TECs), limb amputation and death.

Results of the Protocol Defined Primary efficacy analyses: As the prospective studies B7 and NR13 were interventional studies, the starting point of observation for the primary efficacy endpoint (i.e., effect of therapy on platelet recovery and anticoagulation) was the beginning of study treatment.

Primary efficacy was assessed over a period of approximately 24 days, i.e., between start of therapy with HBW 023 and two weeks after end of therapy. Changes in platelet counts and aPTT over time were compared to each patient's baseline values. Efficacy was assessed in terms of proportion of responders (patients achieving adequate anticoagulation and platelet recovery). A minimum response rate of 20% was defined.

In study B7, 79 of the 82 patients enrolled in all treatment groups were evaluable for the primary efficacy analysis. In study NR13, 98 of the 116 patients enrolled in all treatment groups were eveluable for primary efficacy analysis. Patients were excluded from primary analysis if they had received less that 2 days of treatment or if platelet counts on day 3 and/or 10 were not performed.
In both studies, all patients were included in the safety analysis.

With regard to the primary efficacy criteria, the overall response rate in terms of platelet recovery or maintenance alone was 91.8% in study B7 and 86.1% in study NR13. Effective anticoagulation was achieved in 73.5% and 77.2% of patients in study B7 and NR13 respectively.
The total proportion of responders for the combined response of anticoagulation and platelet recovery was significantly greater (>65%) than the pre-specified limit of 20% (>65%, $p<0.0001$) in both prospective studies. The time course of platelets and aPTT are summarized in the figures on page of this review.

It must be noted, however, that platelet counts in patients with heparin-induced thrombocytopenia usually recover spontaneously, provided that heparin is no longer administered. No direct effct of HBW 023 on speed or extent of platelet recovery was expected, nor found. The time course of platelet counts during the study, in fact, clearly shows that the platelet recovery had already began before treatment with HBW 023 was initiated. The results of the primary efficacy are relevant, however, because they indicate that adequate anticoagulation can be provided by HBW 023 in patients with anti-heparin antibodies without continuation of the underlying immunologic process.

Results of the Clinical Efficacy Analysis and Comparison with Historical Control: The following clinical events were observed for the entire study populations of patients with HAT-II enrolled in

the two prospective clinical trials:

Clinical Endpoints in the total study population

	Study B7		Study NR13	
No. of Patients (%)	82	(100)	116	(100)
Events:				
Death	6	(7.3)	11	(9.5)
Amputation	3	(3.7)	9	(7.8)
New TECs	8	(9.8)	12	(10.3)
Total No.of Patients with Combined Events	15	(18.8)	26	(22.4)

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In order to strenghten the assessment of the effect of treatment on the clinical outcome, a population of patients from the prospective studies presenting with thrombosis (treatment regimen A1 and A2) were compared with an historical control consisiting of patients selected from a registry of HAT-II patients not treated with HBW 023. Since no definite starting point of therapy could be determined for the historical control, the date of laboratory confirmation of HAT-II diagnosis was considered to be the most appropriate starting point for comparing the clinical results. To account for differences in length of observation periods, time-to-event analyses were performed. A maximum period of observation of 60 days from laboratory confirmation of HAT-II was defined.

In **study B7**, the cumulative incidence of combined events (death. amputation or new TEC) since HAT confirmation, compared with the historical control, revealed a statistically significant difference in favor of the HBW 023-treated group (20.4% versus 42.9% four weeks after HAT confirmation, p=0.0142, log-rank test).

The observed difference in the combined endpoint in favor of the HBW 023 group was mainly due to the reduction of the incidences of new TECs (p=0.0786) and deaths (p=0.3117). Reduction in limb amputation in the early post-treatment period would not be espected because ischemic changes already present would not be readly reversible. However, two weeks after HAT type II confirmation, the cumulative incidence of limb amputations was slightly lower in the HBW 023 group compared to the historical control group (3.7% versus 6.4%). Thereafter, the cumulative incidence of limb amputations increased in the historical control group to 14.6% and remained stable in the HBW 023 group (p=0.3864).

None of the prespecified prognostic factors (TECs during heparin

treatment, age, sex, heparin indication, time period between onset of clinical HAT symptoms and laboratory confirmation) appeared to influence the risk of new TECs, amputation, or death. The unadjusted hazard ratio (HBW 023: historical control) was 0.443 (95% CI 0.225-0.871): the adjusted hazard ratio was 0.439 (95% CI 0.211-0.910).

In **study NR13**, 59 patients treated with HBW 023 were compared to the historical control for the combined and individual incidence of death, limb amputations, and new TECs.

Imbalances between HBW 023 patients and historical controls were observed with regard to the number of patients with TECs developing during heparin treatment which was higher in the historical control group compared with prospective study patients (89% versus 70%). However, all 59 patients included in the comparison had TECs at the start of HBW 023 therapy because 10 HBW 023 patients developed a TEC after heparin discontinuation and before HBW 023 therapy.

Eleven patients died during the course of the study resulting in an overall mortality of 9.5%. Causes of death were attributed to the severity of the underlying disease, and none was considered to be related to the study drug. Twelve patients (10.3%) experienced a new TEC, eleven of these during HBW 023 treatment. Nine patients (7.8%) underwent limb amputation during the study period. The incidence of the combined clinical endpoint (death, limb amputation or new TEC) was 22.4% during the entire study period.

When comparing the individual and cumulative incidences of death, new thromboembolic complication, and limb amputation, no statistically significant differences between groups were seen. However, the average combined event rate per patient day during HBW 023 treatment (0.015) was reduced compared to the period between laboratory confirmation of HAT and initiation of HBW 023 treatment (0.035). After cessation of study treatment, the average combined event rate per patient day further decreased to 0.006.

Meta-Analysis: Since the two studies were essentially identical, a meta-analysis of the efficacy and safety data was performed.
A total of 113 patients (54 from study B7 and 59 from study NR 13) with acute HAT-II and ongoing thrombosis (groups A1 and A2) from the two prospective studies were compared to the historical control for the clinical events of death, new TECs and limb amputation.
A numerical difference, not statistically significant (p=0.11),in favor of HBW 023 persisted in the the meta-analysis.

Analyses by First-Selected Treatment: The pre-specified (main) analysis included events occurring over 60 days from from the time of laboratory

diagnosis of HAT-II. However, in both prospective studies, initiation of therapy was delayed by a mean of 1.5 days from the time of laboratory diagnosis. Consequently, the treatment effect of HBW 023 on clinical endpoint was diminished by events occurring before the start of treatment. In both studies, in fact, the average combined event rate per patient day during HBW 023 treatment was reduced compared to the period between laboratory confirmation of HAT-II and end of treatment. In the pooled studies, the average event rate of the combined endpoint per patient day was 0.061 in the pre-treatment interval and 0.007 in the post-treatment interval.

This finding had not been anticipated when the time of laboratory confirmation of HAT-II was selected as starting point for observation. Since no therapeutic effect of HBW 023 could be expected prior to its initiation, an exploratory analysis was performed to compare the incidence of the combined endpoint occurring from the start of HBW 023 treatment in the prospective studies to that occurring after the selection of first treatment following HAT confirmation in the historical control. This analysis also allows to compare HBW 023 treatment with the different treatments used in the historical control group.

In **study B7**, the incidence of the combined endpoints (death, amputation, or new TEC) occurring after the start of HBW 023 treatment to the end of the observation period was significantly lower compared to the historical control adjusted for time of first treatment (n=74). The incidence of any event in the compined clinical endpoint was 13% in the patients compared to 40.3% in the historical control (p=0.0004). The estimated adjusted hazard ratio (HBW 023: historical control) was 0.205 indicating a RR of clinical events of 80%.

Cumulative incidences of new TECs were significantly higher in the historical control group than in the HBW 023 group (p=0.0029). Cumulative death incidences were nominally higher in the historical control group compared to the HBW 023 group (p=0.1283). There was no relevant difference with regard to limb amputation (p=0.8462).

When HBW 023 was compared to other regimens used as first selected treatment, the risk of combined endpoints was significantly lower in the HBW 023 group compared to HAT patients treated with heparinoid (p=0.0004) or with oral anticoagulation (phenprocoumon) (p=0.0125).

In **study NR13**, the incidence of the combined endpoints (death, amputation, or new TEC) was consistently lower in the HBW 023 group than in the historical control group (17.9% versus 21.3% by Day 7, 33.3% versus 40.3% by Day 28); however, the difference was not statistically significant (p= 0.66). The estimated adjusted hazard

ratio (HBW 023: historical control) was 0.80. No statistically significant difference in incidece of clinical events was noted between the HBW 023 group and the individual historical first selected treatments.

The cumulative incidences of combined events occurring in the pooled patient population from studies B7 and NR13 since HAT-II confirmation and since start of therapy are shown in the following table.
Table 1 includes the events occurring in the pooled treated population (n=113) and in the historical control (n=91) since the time of HAT-II confirmnation.
Table 2 include the events occurring in the treated population (n=113) and in the historical control (n=75) since the start of the first selected treatment.

Table 1: Cumulative combined event incidences since HAT confirmation

Time (Days since HAT confirmation) confirmation)	HBW 023 (n=113) No.at Risk	Cumulative Incidence	Historical Control (n=91) No.at Risk	Cumulative Incidence
7	95	16.8%	68	21.5%
14	84	25.7%	49	31.7%
21	67	28.4%	36	36.1%
28	27	28.4%	23	43.1%
35	9	28.4%	14	52.0%
42	5	40.3%	13	55.5%
Log-rank test				

Table 2: Cumulative combined event incidences from start of Therapy

Time (Days since start of therapy)	HBW 023 (n=113) No.at Risk	Cumulative Incidence	Historical Control (n=75) No.at Risk	Cumulative Incidence
7	102	10.6%	55	24.9%
14	92	19.5%	38	36.1%
21	76	21.3%	28	38.0%
28	27	21.3%	20	40.7%
35	9	21.3%	12	47.8%
42	6	21.3%	11	52.2%
Log-rank test				

In the analyses of events occurring since start of therapy, the cumulative incidence of the combined endpoint of new TECs, limb amputations or death was consistently lower in the pooled patients treated with HBW 023 compared to the historical control. The log-rank test showed a significant difference in favor of HBW 023 (p=0.004).

Cumulative incidences of new TECs showed statistically significant difference (p=0.005). Numerical differenbces not statistivcally significant were observed for amputation or death, however the incidence rate of death at 35 days was 8.9% in the HBW 023 group compared to 17.6% in the historical control.

Efficacy of HBW 023 in patients presenting with isolated thrombocytopenia: It was anticipated that patients with HAT-II presenting with isolated thrombocytopenia without ongoing thrombosis (group B) were at lower risk of TECs, and that a lower dose of HBW 023 would be effective for thromboprophylaxis.
However, contrary to expectations, the combined event rate in the pooled group B (n=61) was 28%. Therefore, it appears that the risk for TECs persists in all HAT-II patients for a time despite discontinuation of heparin.

This finding has been clearly emphasyzed in the recent review of Heparin-induced thrombocytopenia (T.E.Warkentin, J.G.Kelton: A 14-year study of heparin-induced thrombocytopenia. Am.J.Med. 1996; 101:502-507). As shown in the following table reproduced from the above report, the risk of TECs appears to be in excess of 50% within 30 days of diagnosis and discontinuation of heparin therapy.

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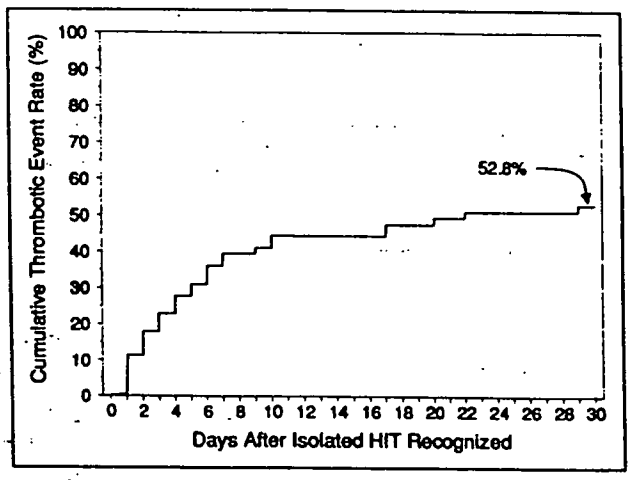

Figure. Cumulative frequency of thrombosis in heparin-induced thrombocytopenia patients presenting with isolated thrombocytopenia. Approximately 50% of heparin-induced thrombocytopenia patients initially recognized with isolated thrombocytopenia developed objective evidence for thrombosis during the subsequent 30-day period. HIT = heparin-induced thrombocytopenia.

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Safety Analysis: A significantly higher rate of documented bleeding events was observed in the prospective study population compared to the historical control. Bleeding of any severity occurred in 30% of patients in study B7, 42% in study NR13 (36% in the combined HBW 023-treated population), and in 15% in the historical control. The majority of bleedings in the HBW 023 group occurred as peri- or post-operative complication or hemorrhage at a disturbed site.

The overall incidence of major bleeding in the treated population was 16% (13% in study B7 and 18% in study NR13) compared to 7% in the historical control ($p=0.008$). No intracerebral (IC) hemorrhage occurred during the study, and none of the observed major bleeding events was fatal. However, the number of patient is small for meaningful assessment of events such as IC bleeding.

Spontaneous major bleedings included GI, GU, URT tract, retroperitoneal and intracavitary bleeding. No significant differences in bleeding incidences were noted among treatment regimens or between younger (< 65 years of age) and older (> 65 years of age) HAT patients or between female and male patients.

It must be noted that patients in the prospective studies, contrary to the historical control, were at high risk of bleeding due to multiple antithrombotic therapy, i.e. HBW 023 plus oral anticoagulant, thrombolytics or antiplatelet agents.

Serious adverse events (SAEs) other than bleeding were reported for 26 patients (32%) in study B7 and in 45 patients (39%) in study NR13. Serious adverse events possibly related to HBW 023 treatment occurred in 9 (11%) and 19 (16%) patients in the two studies respectively. In twenty-one patients (18%), study medication was prematurely terminated due to an adverse event in 8 patients (10%) in study B7 and in 21 patients (18%) in study NR13. All patients who discontinued therapy because of an AE had also experienced a clinical event (death, new TECs or limb amputation).

Two patients in study B7 and 6 patients in study NR13 (4% overall) experienced an allergic reaction during the study period. In none of the three patients, HBW 023 treatment had to be discontinued due to the event, but a causal relationship to the study drug could not totally be excluded.

A total of 38 patients (46%) in study B7 and 49 patients (42.2%) in study NR13 developed IgG antibodies against hirudin, including the three patients who had experienced an allergic reaction. None of the patients developed IgE antibodies. The first positive antibody values

were observed four to six days after start of study treatment. Positive antibody testing persisted at 3 to 10 months after exposure.

The formation of antibodies against hirudin was not associated with reduced hirudin plasma levels or occurrence of clinical events, such as death, new TEC, major bleeding, or allergic/anaphylactic reaction. However, in 5 patients with anti-hirudin antibodies, the HBW 023 maintenance dose had to be reduced by 2-3-fold to maintain a stable aPTT. Thus, one clinically relevant effect of anti-hirudin antibodies might be a possible enhancement of anticoagulant effect of r-hirudin. Daily monitoring of aPTT during HBW 023 treatment is recommended, especially if patients are treated for more than five days.

Five patients with persisting anti-hirudin antibodies were re-exposed to HBW 023 during a repeated treatment course, none of them experienced any allergic reaction.

Foreign Marketing of HBW 023: On March 13, 1997, the European Commission issued a Marketing Authorization for HBW 023 (Refludan) for the treatment of adult patients with heparin-associated thrombocytopenia (HAT-II) and thromboembolic disease mandating parenteral antithrombotic therapy. The recommended initial dose regimen is 0.4 mg/kg bw iv bolus followed by 0.15 mg/kg bw/hr as a continuous infusion for 2 to 10 days or longer if clinically indicated.
Dosage is monitored by aPTT and adjusted as needed to maintain the aPTT at 1.5 to 3.0 times control.
In patients scheduled to receive oral anticoagulation with coumarin derivatives after HBW 023 therapy, HBW dosage is reduced to aPTT of just above 1,5 times control before starting oral anticoagulation. HBW 023 is discontinue when the INR of 2.0 is reached.

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In conclusion, two open-label, historically controlled studies have assessed the efficacy and safety of r-hirudin (HBW 023) in the treatment of HAT-II presenting with thrombosis.

Although both studies showed comparable efficacy of HBW 023 on the primary endpoints of adequate anticoagulant effect and platelet recovery, the two studies were discordant in regard to clinical efficacy endpoints. Whereas a statistically significant difference in favor of HBW 023 treatment compared to historical control for the incidence of clinical events was observed in study B7, only a numerical reduction in the incidence rate of clinical events, not statistically significant, was noted between treated patients and historical control in study NR13. This numerical difference was

enhanced when events occurring after the start of therapy were analyzed, i.e., when events occurring after discontinuation of heparin but before initiation of HBW 023 were excluded. This analysis appears to be clinically valid, moreover, it emphasized the need for early antithrombotic treatment when the risk of TECs appears to be greatest.

The following imbalances were noted among patient populations that may have influenced the clinical outcomes:
- Event occurring on the day of laboratory diagnosis of HAT-II (start of observation period) were not included in the historical control; this resulted in an underestimation of events in the control group.
- Severe thromboembolic events, such as pelvic and iliac vein thrombosis, vena cava thrombosis, and arterial thromboembolism, occurring during heparin therapy were more frequent in patients enrolled in study NR13 compared to historical control.
- More patients in study NR13 than in study B7 had multiple TECs: 53% of the patients with thrombosis had more 2 or more TECs in study B7, compared to 70% in study NR13.
- More than 35% of the patients excluded from enrollment in the two prospective studies (B7 and NR13) were patients with HAT-II and ongoing thrombosis who did not require parenteral anticoagulant therapy. This exclusion criterion was not applied to the historical control. Consequently, some patients with less severe prognosis may have been included in the historical control and excluded from the prospective studies population.

Overall, treatment with HBW 023 reduced the incidence of the clinical endpoint of death by 9%, limb amputation by 4%, new TECs by 17%. The incidence of the combined endpoint was reduced by 27%.

Bleeding complications were increased by the administration of HBW 023: the incidence of any bleeding was increased by 18% and the incidence of bleeding requiring transfusion was increased by 12%.

The incidences of clinical endpoint (treatment failure) and bleeding complications are summarized in the following table.

Incidences of clinical endpoints from start of therapy to end of observation

	Study B7 (N=54)		Study NR13 (N=59)		Combined (N=113)		Hist. Control (N=77)	
Event	N	%	N	%	N	%	N	%
Death	3	6%	8	14%	11	10%	9	12%
Amputation	2	4%	5	8%	7	6%	6	8%
New TECs	3	6%	9	15%	12	11%	19	25%
Combined	7	13%	18	31%	25	22%	30	40%
Bleeding Requiring Transfusion	7	13%	14	24%	21	19%	5	6%
Any Bleeding	16	30%	25	42%	41	36%	12	15%

Summary of Safety Events

Overall, 18/56 (32%) bleeding events were reported (for treatment regimen A1 and A2). Seven (7/56=13%) of these were described as major and 15 (15/56=27%) were described as minor bleeds, respectively. Among major bleeds, none were males, 14% (=5/36) were 65 years old or younger and 22% (=2/9) were on thromboembolytic drug.

A total of 31/56 (=55%) adverse events (AEs) were reported among patients in treatment regimen A1 and A2; 19 of these were described as possibly drug related. Fifteen of the AEs (15/31=48%) were described as serious. Three deaths were reported (none considered drug related). For the historical control group, 10/91 (=11%) major bleeding events (hemorrhage and/or GI hemorrhage) were reported.

The minimum age requirement for entry into this trial is 18 years; the pediatric implication of this drug is therefore not clear.

OVERALL CONCLUSION

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In this reviewer's assessment, the efficacy data in this single study submission provide adequate support for the claim of refludan (lepirudin) effectiveness in the treatment of heparin associated thrombocytopenia (HAT) type II patients.

A. J. Sankoh, Ph. D.
/S/ 4/7/97
Mathematical Statistician

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Concur:
Dr. Huque /S/ 4/7/97
Dr. Smith /S/ 4/8/97

cc: Archival NDA # 20-807
HFD - 180
HFD - 180/Dr. Fredd
HFD - 180/Dr. Talarico
HFD - 180/ Folkendt/Dubeau
HFD - 344/Dr. Lisook
HFD - 720/Dr. Smith
HFD - 720/Dr. Huque
HFD - 720/Dr. Sankoh
HFD - 720 File Copy
Sankoh/x73090/AJS/04-07-97.

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IX. REGULATORY RECOMMENDATIONS

It is recommended that the the application for HBW 023 (Refludan, Lepirudin) for the treatment of patients with HAT-II presenting with thromboembolic complications be approvable, pending the following issues to be addressed by the sponsor:

Labeling: The proposed package insert submitted in the NDA requires extensive revision because it refers mainly to the protocol-specified primary efficacy of adequate anticoagulation and platelet recovery. The efficacy data are based on the results of the single study B7.

The labeling includes dosage recommendations for the use of HBW 023 in conjunction with thrombolytics. The experience in this patient population is very limited, therefore the labeling should state such limitations.

The risk of bleeding should be addressed in greater details with strict recommendations for monitoring in terms of therapeutic range of aPTT and patients risk factors.

Additional revision of the section of Chemistry, Pharmacology and Biopharmacology may be recommended.

Pediatric dosage: HAT-II can affect pediatric patients. The sponsor should collect data in order to provide information on the use of HBW 023 in this patient population.

Treatment of HAT-II presenting with isolated thrombocytopenia: The sponsor should pursue the evaluation of the effective dose regimen indicated for this patient population.

Treatment of patients with "latent HAT-TT": The sponsor should evaluate the efficacy and safety of HBW 023 in this potentially large patient population.

/S/

Lilia Talarico, M.D.

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cc:
NDA 20-807
HFD-180
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 8/18/97 jgw
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